METABOLIC ACIDOSIS AND RESPIRATORY COMPENSATION IN UREMIA DURING HEMODIALYSIS

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1970

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A Thesis Submitted in Partial
Fulfillment of the Requirements
for the Degree of Doctor of Medicine

Yale University School of Medicine
1970

I am greatly indebted to many people who helped with this project. Dr. Howard Levitin freely offered invaluable guidance for all phases of the study. The staff of the Hemodialysis Unit of Yale-New Haven Hospital were always ready to help in obtaining the data. Mr. Kennith Roseman spent many hours maintaining the measurement equipment and assisting in performing the measurements required.

And my wife, Jenifer, typed and proofread far beyond the call of duty.

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INTRODUCTION

In chronic renal insufficiency one of the products of metabolism which accumulates in the body is the hydrogen ion. The phosphoric, sulfuric, and organic acids usually eliminated in the urine accumulate. The respiratory system can and does decrease the hydrogen ion content of the body by decreasing the amount of carbonic acid present. The accumulating hydrogen ions also react with various bases throughout the body. The net result of metabolic production, respiratory elimination, and body buffering is reflected in the blood as chronic, partially compensated, metabolic acidosis. As expected the carbonic acid and blood buffer concentrations are decreased while the concentration of the accumulating anions and hydrogen ion are increased. The adaptive logic of respiratory compensation and body buffering are obvious. Given amounts of unexcretable acids produce lesser increases in hydrogen ion concentration and the organism is protected from the potentially fatal effects of increased hydrogen ion concentration.[1,2,3]

Respiratory compensation and buffering have been extensively studied in the past two decades in an attempt to quantitatively describe the phenomena and define the mechanisms involved. Patients receiving periodic hemodialysis for chronic renal insufficiency have many characteristics which make

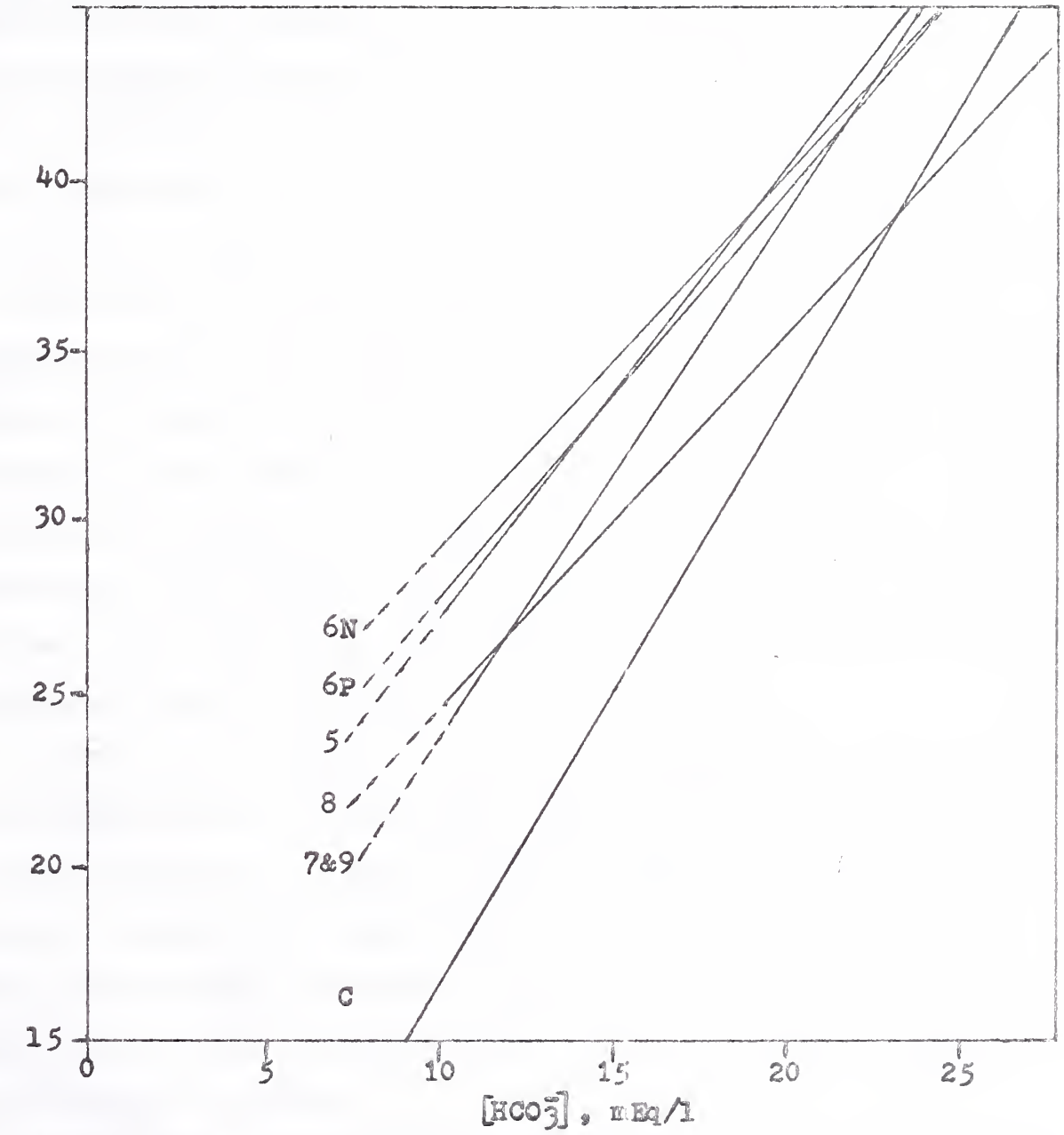
them particularly suited for studying the reactions to changes in acid-base status. Their kidneys no longer excrete significant amounts of acid. They are repeatedly subjected to a changing acid-base status during therapy and can serve as their own controls. Painless sampling of arterial blood is available. In addition the data obtained might be useful to the clinicians responsible for the care of the patients studied. For these reasons it was decided to measure the acid -base parameters of the patients treated by the Hemodialysis Unit of Yale-New Haven Hospital and the respiratory response to the changes in those parameters as reflected by the carbon dioxide tension in the arterial blood(pCO_2).

PREVIOUS INVESTIGATIONS

Several schemes of analyzing and interpreting the basic acid-base parameters as measured in the blood have been proposed. Most important for the studies presented here is that the formulation used and the control data available define the expected respiratory response(pCO_2) for a given degree of metabolic acidosis. One proposal[4] compares the measured pCO_2, $[HCO_3^-]$, and $[H^+]$ in individuals to data obtained from control groups where only one primary change in acid-base balance is present. Four studies have reported control data for metabolic acidosis. The data are depicted graphically in Figure 1 as regression lines of pCO_2 on $[HCO_3^-]$ for the groups studied.

Moller[5] measured arterial blood samples in patients with chronic renal disease before they received therapy. The stability of the acid-base status at measurement was not determined. Clinical respiratory disease was not present. Lennon and Lemann[6] obtained regression lines from normals loaded with NH_4Cl and $NaHCO_3$ and from fifty patients with chronic renal disease not receiving treatment. Their subjects were studied on a metabolic ward with reportedly stable acid-base parameters when the reported data were obtained. The normals and patients yielded lines statistically the same though the slope of the patients' line was somewhat steeper. All samples were venous blood which tends to have an increased $[H^+]$ secondary to increased pCO_2. This systematic error would tend to decrease the slope of the

Figure 1 - Untreated Chronic Metabolic Acidosis



Complete Compensation Isopleth			
C. pH= 7.40	$pCO_2 = + 1.68 [HCO_3^-]$		
Patient Regression Lines			
5. Moller	$pCO_2 = 14.3 + 1.31 [HCO_3^-]$	S.E.=±5.5	
6P. Lennon&Lemann	$pCO_2 = 15.8 + 1.20 [HCO_3^-]$	Venous	
7. Albert et.al.	$pCO_2 = 8.4 + 1.54 [HCO_3^-]$	S.E.=±1.1	
9. Elkinton	$pCO_2 = 8.8 + 1.51 [HCO_3^-]$	S.E.=±4.0	
Normal Regression Lines			
6N. Lennon&Lemann	$pCO_2 = 18.3 + 1.10 [HCO_3^-]$	Venous	
8. Elkinton et. al.	$pCO_2 = 13.8 + 1.09 [HCO_3^-]$		

regression lines obtained. Albert et.al.[7] studied patients with metabolic acidosis secondary to diarrhea, diabetes, and renal disease. Arterialized capillary blood was obtained before treatment on admission to the hospital. Patients were not reported if neurologic or respiratory disease was suspected radiologically or clinically, nor if the pH were below 7.10. Elkinton[8] studied normals after three and five days of NH_4Cl loading. The parameters were stable between the two days. He also summarized retrospectively[9] the data of patients with chronic uremia seen by a metabolism service. Arterial or arterialized capillary blood was obtained before treatment and patients were included only if pCO_2 was below normal. All patients were within the expected range of the extrapolated regression line for normals.

Despite the range of patients, measurements, and controls for complicating disorders and rapid shifts in acidosis, the regression lines for the studies are remarkably similar. The lower slopes of the lines obtained in normals are apparently not significantly different from the lines of patients suggesting that both groups respond similarly to given degrees of metabolic acidosis.

The line of "perfect" compensation for metabolic acidosis is arbitrarily defined as the pCO_2-HCO_3^- relationship predicted by the Henderson-Hasselbalch equation, if the respiratory response to acidosis maintains a concentration of hydrogen ion

of 40 nMol/l. None of the patient or normal groups studied show complete compensation.

The increased hydrogen ion concentration of metabolic acidosis can be corrected by the administration of alkali or in diabetes, insulin. Soon after such therapy was first attempted, it was discovered that restoration of blood buffer or HCO_3^- concentrations to normal often led to a respiratory alkalosis, as hyperventilation and low pCO_2 persisted despite the decrease in $[H^+]$ to levels below normal. Peters[10] first reported that the increase in the CO_2 content of blood to normal levels during therapy for diabetic or uremic acidosis was not accompanied by the rapid return of aveolar pCO_2 to normal.

Winters et. al.[11] summarized the findings of the investigations following Peters. Included are patients with diabetic, uremic, and diarrheal acidosis, and normals spontaneously correcting an experimentally induced NH_4CL acidosis. The many investigators sampled blood before and at various intervals during HCO_3^- repletion. Many of the studies used venous blood with its higher pCO_2 and lower pH. Two thirds of the more than 100 patients reported demonstrated a depressed pCO_2 (less than 40mmHg) in the first sample obtained with a pH of 7.35 or more. Many of the patients had alkalemia despite normal to decreased blood $[HCO_3^-]$. Three NH_4CL loaded normals had respiratory alkalosis two days after acid loading had ended. In these groups

then, some degree of decreased pCO_2 persisted despite the removal of acidemia as a respiratory stimulant. Direct measurement of ventilation or CO_2 production was not done in these studies. Thus, the persistent decrease in pCO_2 may reflect decreased production or increased efficiency of elimination, and not simply persistent hyperventilation. Other causes of hyperventilation such as hypoxia, respiratory disease, and neurologic disease were not eliminated. Measurements were sometimes made after rapid alkali loads at a time when equilibrium between blood and extracellular fluid may not be present.[12] On the other hand the failure to eliminate patients who before treatment exhibited no compensatory hyperventilation tends to underestimate the frequency of the phenomenon.

Further evaluation of the acute effects of correcting acidosis with alkali has been done in patients receiving hemodialysis for maintenance in chronic renal failure. Many of the studies include patients with obvious CO_2 retention (pCO_2 greater than 40mmHg) relative to their acidosis. These patients usually were reported as having clinical respiratory disease and are not considered below, as changes in their pCO_2 values are likely to be produced in part by changes in their lung function independent of respiratory drive. Of the six patients studied by Weller et. al.,[13] three developed respiratory alkalosis

by the end of their dialyses. Two others had normal (H^+) and persistently low pCO_2. One with a pre-dialysis (HCO_3^-) of 4mEq/l still had a partially compensated metabolic acidosis after dialysis. The six had a mean increase in pCO_2 of 2mmHg while the pH rose 0.18 units. Sanchez et. al.[14] reported two patients with partially compensated metabolic acidosis before dialysis. One developed respiratory alkalosis during all five dialyses studied. The other showed minimal changes in pCO_2, while his pH returned to normal at still depressed (HCO_3^-). Of the four patients studied by Pauli et.al.,[15] three developed respiratory alkalosis before dialysis was complete and the other had no change in any of the parameters of acid-base balance during dialysis.

Cowie et.al.[16] studied seven patients with respiratory compensation before dialysis. One developed pulmonary edema during dialysis with CO_2 retention and hypoxia. Of the other six, four developed respiratory alkalosis by the end of dialysis. In these subjects pCO_2 was essentially unchanged during dialysis. The remaining two subjects had incomplete correction of the (HCO_3^-) to levels still below 16mEq/l. They maintained their pCO_2 at levels low enough to result in normal pH values at the end of dialysis. This degree of compensation was associated with greater depression in the pCO_2

than the studies in Figure 1 would predict. In both subjects pCO_2 increased during dialysis but not in proportion to the increase in $[HCO_3^-]$. All of the dialysis studies above used HCO_3^- in the bath as base with the pH maintained by bubbling through carbon dioxide gas.

Earnest et.al.[17] measured the acid-base parameters at hourly intervals during dialysis. All of his fourteen patients had metabolic acidosis with respiratory compensation before the thirty-nine dialyses studied. Maintenance on two eight hour dialyses per week and strict low protein diets was associated with a group mean $[HCO_3^-]$ of 21.4mEq/l before dialysis. Compensation was complete in many patients with a group pCO_2 of 32mmHg and a pH of 7.43. During dialysis with bath concentrations of acetate of 35mEq/l the pH was significantly increased by two hours and the $[HCO_3^-]$ by the fifth hour. The mean pCO_2 was within 1mmHg of the pre-dialysis mean at all times during dialysis. At seven hours the mean for the group was respiratory alkalosis. In six patients tidal volume, respiratory rate, and minute ventilation were measured. All showed hyperventilation which varied only slightly and in both directions during dialysis. The pCO_2 varied by small amounts in a direction appropriate for the small changes in ventilation measured, thus demonstrating the absence of major changes in the production or efficiency of removal of CO_2 during dialysis.

None of the studies above reported the arterial oxygen tension (pO_2) of the subjects. Earnest et.al.[17] and Cowie et.al.[16] both stated that the oxygen saturation was "normal" and the latter reported that oxygen administration did not produce hypoventilation in his subjects, but neither report the data or methodology. The neurologic state of the subjects was not reported, but all investigators stated the respiratory condition of the patients.

From the studies above it is apparent that the increased ventilation of partially compensated metabolic acidosis often persists following acute correction of the acidemia. The assumption that pCO_2 measured in the blood is reflecting ventilation and respiratory drive is confirmed by Earnest et.al.[17] Since after dialysis the pH is normal or high in the blood, the pCO_2 low, and the pO_2 "normal", these patients are hyperventilating without known chemical stimulation of peripheral receptors.

Other causes for the persistent hyperventilation exist. Many respiratory disorders lead to hyperventilation without chemical stimulation of respiration.[1] Assuming normal lungs by X-ray the most likely disorder in uremia is mild congestive heart failure. Fluid removal with stable blood pressure would in general tend to improve the disorder during dialysis. Uremia itself may be interfering with normal respiratory regulation. Uremia does not interfere with the normal respiratory response to increasing

pCO_2.[18-20] Compensation for acidosis is not impaired according to Lennon[6] and Elkington[8]. Henderson et.al.[18] reported in abstract form that chronic uremics had decreased compensation for acidosis compared to normal NH_4CL loaded subjects and "acute" renal failure patients. The study was not reported in full and does not separate the effects of chronic uremia from those of chronic acidosis. Pauli and Reubi[20] found ventilation in chronic uremia to be much less than predicted for the level of acidosis. The prediction was based on the weighted sum of changes in blood and CFS hydrogen ion concentrations. The latter was calculated from constants obtained from normals with no evidence that they held for the patients studied. All calculations were based on the "Reaction Theory" of respiratory regulation.[21]

In the absence of direct evidence that respiratory reflexes or their integration are disrupted in uremia, most investigators proposed that the relative isolation of the central nervous system and CSF from changes in blood $[HCO_3^-]$ and $[H^+]$ maintained a relative acidosis at the medullary chemoreceptors during alkali administration.[22] Measurement of the CSF pH in chronic uremia during acidemia has in most cases failed to demonstrate a CSF acidosis.[15,23-26] The CSF pH was normal in these studies because $[HCO_3^-]$ was not depressed proportionally in the CSF and blood. Blood and CSF pCO_2 were decreased by similar amounts.

Cowie et.al.[16] reported an acidotic CSF in one of the uremic patients he studied. During subsequent periods of increasing HCO_3^- in that patients blood, his CSF HCO_3^- was found to follow the blood very closely instead of remaining stable as usually demonstrated. Schwab[27] arbitrarily grouped his acidotic patients according to blood pH and found the "severely" acidotic group to have a mean CSF pH greater than control subjects. Rosen et. al.[28] found a mean CSF pH for 10 "acute" renal failure patients that was 0.09 units lower than his control mean. The duration of the acidosis, previous alkali therapy, and the statistical significance of the differences was not reported. Chazan et.al.[29] found identical mean CSF hydrogen ion concentrations in dogs before and after one and two weeks of metabolic acidosis produced by oral HCl loading. The reported measurements were obtained during periods when the dogs were in a steady state of acidosis as demonstrated by serial blood samples.

The relative impermability of the CSF to blood HCO_3^- implied by the studies above is confirmed by measurements in animals[30,31] and man[15,16,23,25,27,28,32,33] during acute changes in blood HCO_3^- concentration. CSF pCO_2 on the other hand, promptly reflects changes in arterial pCO_2 produced by CO_2 inhalation or hyperventilation.[34] Indeed, during acute changes in the blood HCO_3^- it is the secondary changes in blood and CSF pCO_2 which determine any change in

the CSF pH. As the secondary changes tend to oppose the pH in the blood, they may lead in the CSF with its stable $[HCO_3^-]$ to a change in pH opposite to the blood, the "paradoxical" change in CSF pH. This has been observed in normal man [22,23] and animals [30,31] consistently within 1 hour of the infusion of large amounts of acid or HCO_3^-. The pH change was found to be secondary to pCO_2 changes in the CSF which followed similar changes in the blood. The "paradoxical" change also occurred when severe non-renal acidosis was treated with rapid HCO_3^- infusion.[32] Over the several hours of hemodialysis little HCO_3^- enters the CSF and again changing pCO_2 determines the pH. In two studies CSF pH was found to change by small amounts in either direction during dialysis as CSF pCO_2 followed the small changes in blood pCO_2.[15,16] In two subjects[16] the blood and CSF pCO_2 changed by much different amounts and CSF pH was determined by the latter. When the mean blood pCO_2 did not change,[27] then the mean CSF pCO_2 and pH were stable.

CSF pCO_2 is normally 7-10mmHg higher than in arterial blood in humans [15,23,24,26-8,32-3] and dogs.[29] The pCO_2 in jugular venous blood is equal to or slightly more than in the CSF.[23,24,33] Most investigators have presumed that the metabolic rate, R.Q., and blood flow of the brain maintain the arterial-CSF pCO_2 difference and that changes in those variables may change CSF pCO_2 independently of

the arterial pCO_2. The arterial-CSF difference has been reported as normal in metabolic acidosis.[15,27,28,35] The decreased gradient in the study of Bradley and Semple[23] was not statistically significant. Posner et.al.[24] include some subjects with acidosis who have lower pCO_2 in the CSF than in the arterial blood. This unexplained and unique finding casts doubt on the validity of the mean decrease in the arterial-CSF pCO_2 difference they reported. Mitchell et.al.[26] found a small, statistically significant decrease in the pCO_2 gradient in metabolic acidosis. The gradient was unchanged in dogs during steady state acidosis from HCL administration.[29] Lumbar CSF does not detect pCO_2 changes present for up to 20 minutes in the cisternal fluid in man[34] although the (HCO_3^-) is the same in each. This makes all but two of the studies above difficult to evaluate[27,29] as any ventilatory change induced by the sampling procedures might produce changes in the arterial-lumbar CSF difference that did not occur in the arterial-cisternal CSF difference. As stated previously, the difference is not changed by alkali therapy for chronic metabolic acidosis.

Mitchell et.al.[26] proposed a theoretical construct to explain the ventilatory responses of acidotic and anoxic[15, 36] subjects before and after correction of the blood abnormality. During the chronic state ventilation is high becaused increased stimulation of the peripheral

chemoreceptors is added to normal stimulation of the central receptors in CSF of normal pH. Acute correction of acidosis or anoxemia reduces peripheral activity and ventilation. The arterial pCO_2 increases as ventilation decreases leading to increased CSF pCO_2 and acidosis in the CSF. The central acidosis leads to increased central stimulus levels and ventilation is fixed at an intermediate level still above normal until active transport slowly restores CSF HCO_3^- and pH to normal. The studies in altitude acclimatization[36] demonstrate the predicted changes in ventilation, arterial blood, and the CSF in four normal subjects.

In uremic acidosis treated by hemodialysis the ventilation did not decrease, and the arterial pCO_2 did not rise.[17] Rosen et.al. confirmed the above in "acute renal failure" and in addition demonstrated a constant arterial CSF pCO_2 difference and no change in CSF pH. Twenty-four hours after dialysis the blood acid-base status was unchanged (respiratory alkalosis) from immediately following dialysis. The CSF HCO_3^- increased over this period while its pCO_2 was stable and the pH was increasing slightly to above the mean for normals. The hyperventilation had persisted despite an increasing CSF pH and a stable alkalemia in the blood. This study attempts to verify the results of the two investigators above in a different laboratory and to document the pO_2, which has not been done before.

METHODS

Subjects

Appendix I gives identifying data for the patients studied.

All eight of the patients receiving semi-weekly hemodialysis for chronic renal insufficiency during the period June through July of 1969 were studied. All had urinary outputs of 400ml/day or less at the time of study. Renal insufficiency had required dialysis for from 6 months to 2 years. All but patient 5 received peritoneal dialysis before beginning chronic hemodialysis.

The patients were all maintained on low protein, low salt diets with fluid restriction. Patient 7 regularly ingested excessive amounts of salt and water between dialyses. None of the patients was obese. None of the patients had prescriptions for $NaHCO_3$ between dialyses, but patient 8 probably received some intermittently.

All but patient 4 had experienced heart failure with pulmonary symptoms and radiologic signs. At the time of study chest X-rays were obtained in seven of eight patients. Patients 1,2,4,5, and 6 showed no pulmonary congestion or edema or pleural effusions. In these patients there were no physical signs of the above. Patient 3 had pulmonary congestion and was only a few days past an episode of pulmonary edema at the time of

the first dialysis studied. By the time later measurements were made the chest was clear clinically and radiologically. Patient 7 had chronic congestive changes with varying amounts of edema and effusion correlating well with the estimated excess of fluid present. On two occasions this patient had clinical signs of pulmonary edema at the beginning of dialysis. Patient 8 had no clinical signs of pulmonary edema but chest films were not obtained. None of the patients had clinical signs or radiologic signs of acute or chronic respiratory disease except for some isolated calcifications in the upper lobes. All but patient 4 were on digitalis therapy.

The central nervous system of all subjects but patient 8 was intact clinically. Patient 8 had Parkinson's syndrome and chronic disorientation with EEG changes consistent with metabolic encephalopathy. No cranial nerve dysfunction or abnormal respiratory rhythms were present.

Other than tachypnea (mean rate of 25/min.) no changes in respiration indicated the extent of hyperventilation. Kussmaul and periodic respirations were not present.

Patients 1,2,3,6, and 7 had smoked cigarettes in the past. All but patient 6 had stopped by the time of the study.

Procedure

Pre-dialysis samples were obtained from the inlet tubing of the hemodialysis apparatus while the coil was filling with blood and before any blood had returned to the patient. Post-dialysis samples were obtained from the inlet tubing $5\frac{1}{2}$ hours ($\pm\frac{1}{4}$ hours) later, approximately $\frac{1}{2}$ hour before termination of dialysis. The pair of samples was obtained for three dialysis runs on each patient over a period of two weeks (6/13/69- 6/27/69) except for one pair obtained on one patient one month later.

Many of the patients were found to have low pO_2 levels during the period above and, in an attempt to eliminate respiratory drive from chemoreceptors due to oxygen lack, seven patients were given humidified oxygen by perforated mask during dialysis. One elderly, disoriented patient (8) was unable to cooperate or to give informed consent and was not included in this part of the study. The dead space and discomfort of the mask were negligible. Oxygen administration was begun a few minutes after the pre-dialysis sample had been obtained and was continued until after the post-dialysis sample had been drawn. The oxygen was discontinued when the patients had lunch for twenty minutes after $2\frac{1}{2}$-3 hours of dialysis and occasionally for a few moments to allow readjustment of the mask fit. At least one hour of uninterrupted

oxygen administration preceded the post-dialysis sample. Blood was obtained at intermediate times on several occasions during oxygen administration.

Sampling involved no pain or participation by the patients. Previous samples had been obtained with similar methods while methodology was being designed and patients routinely ignored the presence of the investigator during the studies. Many of the patients slept intermittently during dialysis and were not disturbed during sampling. None of the patients was complaining of pain from the implanted needles at the time of sampling and all were at rest supine in bed with the head elevated from a few to sixty degrees.

The routine of dialysis was not altered in any way except as outlined above. Weekly active limb exercise in bed was performed during one half of the studied dialyses. Heparin, protamine, and antihypertensives were routinely given. Talwin and Darvon were given as indicated. All patients were alert or in a light, easily interrupted sleep during dialysis. Patient 8 was awake but chronically disoriented. One unit of packed cells and up to 500 ml. of isotonic saline were given as dictated by the hematocrit and blood pressure respectively. The lowest brachial pressure recorded for the study was 110/70. No serious complications of renal failure or dialysis developed acutely during the periods reported. On one

occasion thrombosis of a patient's vein central to the return line led to stasis and the study was repeated. Dialysis was discontinued for one half hour during one of the dialysis periods reported because of separation of the tubing three hours into the run. The patient (5) was restarted after replacement of the estimated blood loss of one unit and the data are reported.

The machine specifications and bath composition are included in Appendix II.

Measurements

pH, pCO_2 & pO_2 8ml. of blood was obtained in one 10 cc. glass syringe with approximately 0.1ml of Sodium Heparin (10^4 units/ml.) in the dead space of the syringe and #19 needle. The inlet flow was decreased from an average of 200ml/min to 20ml/min during sampling to decrease the negative pressure needed to obtain the blood and tending to draw air into the syringe. Very rare small air bubbles were exhausted and the needle tip immediately buried in a rubber stopper. The sample was then placed in an ice water bath. All measurements were completed within one hour of sampling.[37]

The pH of whole blood was measured using the IL-Glass pH Electrode and the IL-113 Blood Gas Analyzer at a constant temperature (IL-127 Constant Temperature

Bath) of 37 degrees C. The electrode was standardized with Na-K phosphate buffers (IL References Buffers) with pH at 37 degrees C. of 7.384 and 6.84.[37,38] Each sample waa measured repeatedly until the pH of two successive measurements was within 0.005 units. Eighty per cent of the samples were measured only twice and only three samples required four measurements. The mean pH of the repeating measurements to the nearest 0.01 units is reported. The oral temperature of the patients measured at various times during dialysis was within one degree of 36 degrees C. at all times. Blood temperature was assumed to be within one degree C. of the temperature of measurement in vitro and no correction (maximum of 0.015pH units) for the difference was attempted.[37,39] Blood pH was assumed to equal plasma pH. The correction for the "suspension effect" of Severinghaus et.al.[40] was not applied as it is small (0.01pH units), was derived using a different electrode, and was found in blood with normal hematocrit. The change in whole blood pH was found to be negligible in one hour on ice, the maximum observed in two hours in leukemic blood being -0.015pH units.[37]

The whole blood pCO_2 was measured on the same instrument with the IL PCO_2 Electrode Assembly with teflon membrane at 37 degrees C. and ambient air pressure.[38]

Ambient barometric pressure was obtained from the Pulmonary Function Laboratory of Yale-New Haven Hospital. Calibration of the electrode was performed with analyzed N_2-CO_2 gas mixtures (IL Analyzed Gases) with 5.39 and 10.09% CO_2. Repeated measurements on the same sample were reported as the mean of two values within 0.5mmHg rounded to the nearest mmHg. No significant increase in blood pCO_2 occurs in whole blood stored on ice in one hour.[37] Again the maximum correction for the observed difference of blood temperature from 37 degrees C. is small (0.6mmHg) and no correction was applied.[41]

Whole blood pCO_2 was measured on the above instrument with the IL PO_2 Electrode (Ag-AgCL) at atmospheric pressure and 37 degrees C. Calibration of the electrode was done with the 5.39% CO_2-N_2 gas mixture (0% O_2) and room air (20.93% O_2). PO_2 was reported as the mean of two repeated measurements with 1mmHg multiplied by 1.02, the correction for measured tensions in liquids to gas tensions.[38] Good correlation has been observed between this method and tonometry.[42] The decrease in pO_2 is 2mm/hr in blood stored on ice in the physiologic range of pO_2.[43] For pO_2 greater than 150mmHg, room air was still used for calibration, the error due to electical extrapolation not influencing the qualitative significance of the data required. The loss in pO_2 is increased over time at higher pO_2 levels.[43]

CO_2 Content Blood was obtained in the same manner as above with another 10cc glass syringe and needle. The plunger of the syringe was dipped in mineral oil. No air bubbles were observed in these samples. The sample of about 6 ml. was promptly injected under 2cm of oil into a 10cc. Vacutainer tube. The sample was immediately placed unstoppered on ice. Measurement was complete within one hour of sampling. The two samples were drawn within 30 seconds of each other and in both orders.

Plasma CO_2 content was determined on the Thomas Manometric Apparatus by the method of Van Slyke.[44,45] Blood was centrifuged for 10 minutes at 5000rpm at room temperature[46] immediately before measurement. Loss of CO_2 in undisturbed blood under oil is negligible in 1½ hours.[47] The mean of two repeated measurements within 0.3mMol/l (0.6vol%) is reported.

Electrolytes Na, Cl, and K were measured by the clinical laboratory of Yale-New Haven Hospital on serum obtained by Vacutainer from the inlet tubing within 10 minutes of the samples taken above.

Hematocrit and Weight Hematocrit and weight of patients in gowns was obtained before and after dialysis by the staff of the Dialysis Unit.

Method Validation

The samples of blood drawn from the inlet tubing of the dialysis machine were assumed to be arterial blood. When a saphenous vein graft joining the radial artery and brachial veins was punctured by the dialysis needles, the blood obtained must have come entirely from the radial artery assuming proximal veins were patent. When the radial artery is sutured directly to a forearm vein in situ, tributaries of the vein punctured are still intact. It is doubtful that flow in these tributaries is toward the larger vein as the main veins are pulsatile and greatly distended by their high flow and pressure. In two patients with radial-antebrachial fistulas and pO_2 levels below 70mmHg, "arterialized" venous blood was obtained by venipuncture after heating the opposite forearm in water at 45 degrees C. for 15 minutes.[48] Both samples had lower pH (0.008 units), higher pCO_2 (2.5mmHg), and lower pO_2 (10mmHg) than samples obtained simultaneously from the inlet tubing. Simultaneous femoral artery and inlet tubing samples obtained from one of the patients had identical pH, pCO_2, and pO_2 values. The blood from the inlet tubing seems to be arterial.

The validity of the three measures of acid-base balance was checked by comparing the calculated CO_2

content with the measured CO_2 content of 26 samples obtained on the patients at various times during dialysis. Calculated CO_2 content was read from the nomogram of Siggaard-Andersen[49] using the measured pH and pCO_2. The mean difference (calculated - measured CO_2 content) was 2.0 mMoles/l with S.D. of $\pm$1.50 and was different from zero ($p<.01$). The difference did not depend on the pCO_2, pH, or CO_2 content of the samples. The data are shown in Appendix III.

Six samples for pH, pCO_2, and pO_2 were drawn in duplicate and measurements were carried out by the Pulmonary Function Laboratory of Yale-New Haven Hospital and the experimenter. The pH was always within 0.01 units and the pO_2 within 2mmHg with no consistent direction to the differences. The pCO_2 was consistently higher when measured by the experimenter despite the close agreement in pH. The difference ranged from 2-4mmHg.

During and soon after the validation measurements the pCO_2 system developed mechanical and electrical difficulties. The consistent difference in pCO_2 measurements between the probably failing system of the experimenter and the hospital laboratory was of a direction and order of magnitude that would overestimate a calculated CO_2 content by the amount reported above. The error was therefore assumed not to be from systematic error

in pH or total CO_2 content. All pCO_2 results were derived from the nomogram using the measured pH and CO_2 content of the samples.

Calculations

The Siggaard-Andersen nomogram[49] was used to find the pCO_2 using the measured CO_2 content and pH. The nomogram graphically represents the rearranged Henderson-Hasselbalch equation:

$$pCO_2 = \frac{[CO_2 \text{ Content}]}{S\left[10^{(pH-pK)} + 1\right]}$$

where:

$$S = \frac{[\text{Dissolved } CO_2 + H_2CO_3]}{pCO_2}$$

The variation of pK with pH[37] is taken into account by the nomogram. The variation of pK and S with temperature is small within one degree C. and can be ignored.[37] The HCO_3^- concentration was calculated using the derived pCO_2 and S=0.0306mMole/l/mmHg.

$$[HCO_3^-] = CO_2 \text{ content} - S(pCO_2)$$

As reported below many of the patients had low pO_2 and pCO_2 as measured in the arterial blood breathing room air and thus, demonstrated an increased aveolar-arterial difference in pO_2. Any change in the disorder producing the increased aveolar-arterial difference during dialysis might change the difference. The change in the difference ($\Delta(A\text{-}a)Dp O_2$) was estimated from the

formula below derived from the equation for mean aveolar pO_2.[1] The derivation is in Appendix IV.

$$\Delta(A\text{-}a)DpO_2 = -\left[\Delta P_{aO_2} + 1.2(\Delta P_{aCO_2})\right]$$

where:

ΔP_{aO_2} = Post-dialysis arterial pO_2 - Pre-dialysis arterial pO_2

ΔP_{aCO_2} = Post-dialysis arterial pCO_2 - Post-dialysis arterial pCO_2

The oxygen saturation of blood was read from the nomogram of Severinghaus[38]. Corrections for temperature (assumed constant over dialysis) and pH were applied.

Statistical evaluation was by "t" test.[50]

RESULTS

Table 1 summarizes the mean changes in hematocrit, electolytes, and weight in the eight patients during the twenty-four dialyses studied. Individual data are presented in Appendix V. The stable hematocrit suggests that no major hemolysis or hemoconcentration takes place or that the two processes are balancing each other.

TABLE 1

	Pre-dialysis	Post-dialysis	Change	"t" test
Weight, lbs.	-	-	-4.05	$p<.001$
Hematocrit,%	18.4	19.4	+1.0	$p>.1$
Hematocrit *	19.4	19.2	-0.2	$p>.6$
Na^+, mEq/l	136.3	134.0	-2.3	$p<.05$
Cl^- "	98.2	95.9	-2.3	$p<.05$
K^+ "	5.8	3.8	-2.0	$p<.001$
HCO_3^- "	16.1	20.9	+4.8	$p<.001$
Anion Gap ($Na-K-Cl-HCO_3$)	27.8	21.0	-6.8	$p<.001$

*Excludes patients transfused during dialysis

Table 2 shows the means and changes in pO_2 and acid-base measures during dialysis on room air. The means are from the eight patients studied on three different days each. The values in parentheses are the pre-dialysis and 5th hour means of Earnest et. al.[17] The mean change in pCO_2 during dialysis is a small increase of doubtful statistical significance. Patient 8 with cortical and basal ganglion dysfunction did not receive O_2 during the second part of the study. As is shown in Table 3, if patient 8, whose pCO_2 consistently fell

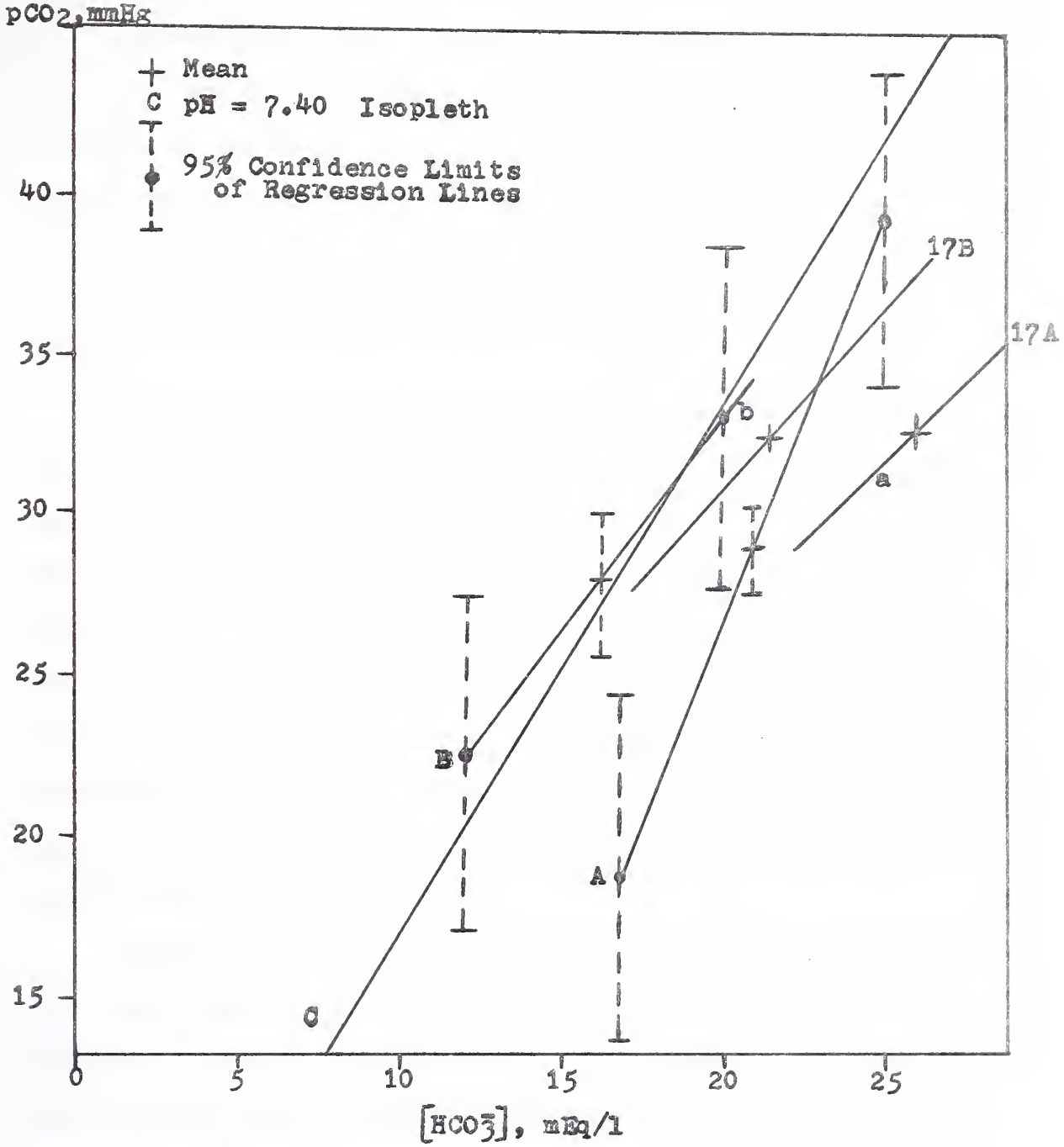
during dialysis, is eliminated, then the mean change in pCO_2 (+1.33mmHg) is significant at the 0.05 level. During 11 of 24 dialyses (8 of 21 eliminating patient 8) no change or a decrease in pCO_2 was recorded. Of eight patients only one showed an increase in pCO_2 during all three dialysis periods studied. The maximum increase in pCO_2 was 5½mmHg.

TABLE 2

	Pre-dialysis	Post-dialysis	Change	"t"test
pH, units	7.39(7.44)	7.49(7.51)	+0.10	p<.001
$[H^+]$, nMol/l	41.1	32.8	-8.3	p<.001
$[HCO_3^-]$, mEq/l	16.05(21.39)	20.90(24.95)	+4.85	p<.001
pCO_2, mmHg	27.88(32.26)	28.75(32.06)	+0.87	p=.20
pO_2, mmHg	73.4	74.8	+0.5	p>.70
O_2 Sat.,%	93.9	95.3	+1.4	p<.01

Figure 2 shows the pCO_2 - $[HCO_3^-]$ relationship for the group before and after dialysis. The regression lines and correlations are computed from the mean of the three pCO_2 and $[HCO_3^-]$ measurements for each of the eight patients. The pre-dialysis line falls well to the right of the lines found previously in metabolic acidosis (Figure 1) indicating that lower levels of pCO_2 are maintained in general by this group for any given level of HCO_3^-. All of the individual data points fall within 2 S.E.'s of at least one of the studies in Figure 1. The slopes from previous studies and the pre-dialysis line are much the same.

Figure 2 - Pa_{CO_2} and $HCO_3^-{}_a$ Before and After Dialysis



Present Study - Regression Lines(N=8)

B	Pre-dialysis	$pCO_2 = 5.3 + 1.41 [HCO_3^-]$	r=0.77	p<.05
A	Post-dialysis	$pCO_2 = -25.7 + 2.61 [HCO_3^-]$	r=0.92	p<.01

Earnest et.al.[17] - Regression Lines(N=14)

17B	Pre-dialysis	$pCO_2 = 7.85 + 1.15 [HCO_3^-]$
17A	Post (7 hrs.)	$pCO_2 = 7.01 + 0.99 [HCO_3^-]$

Rosen et. al.[28] - Means(N=10)

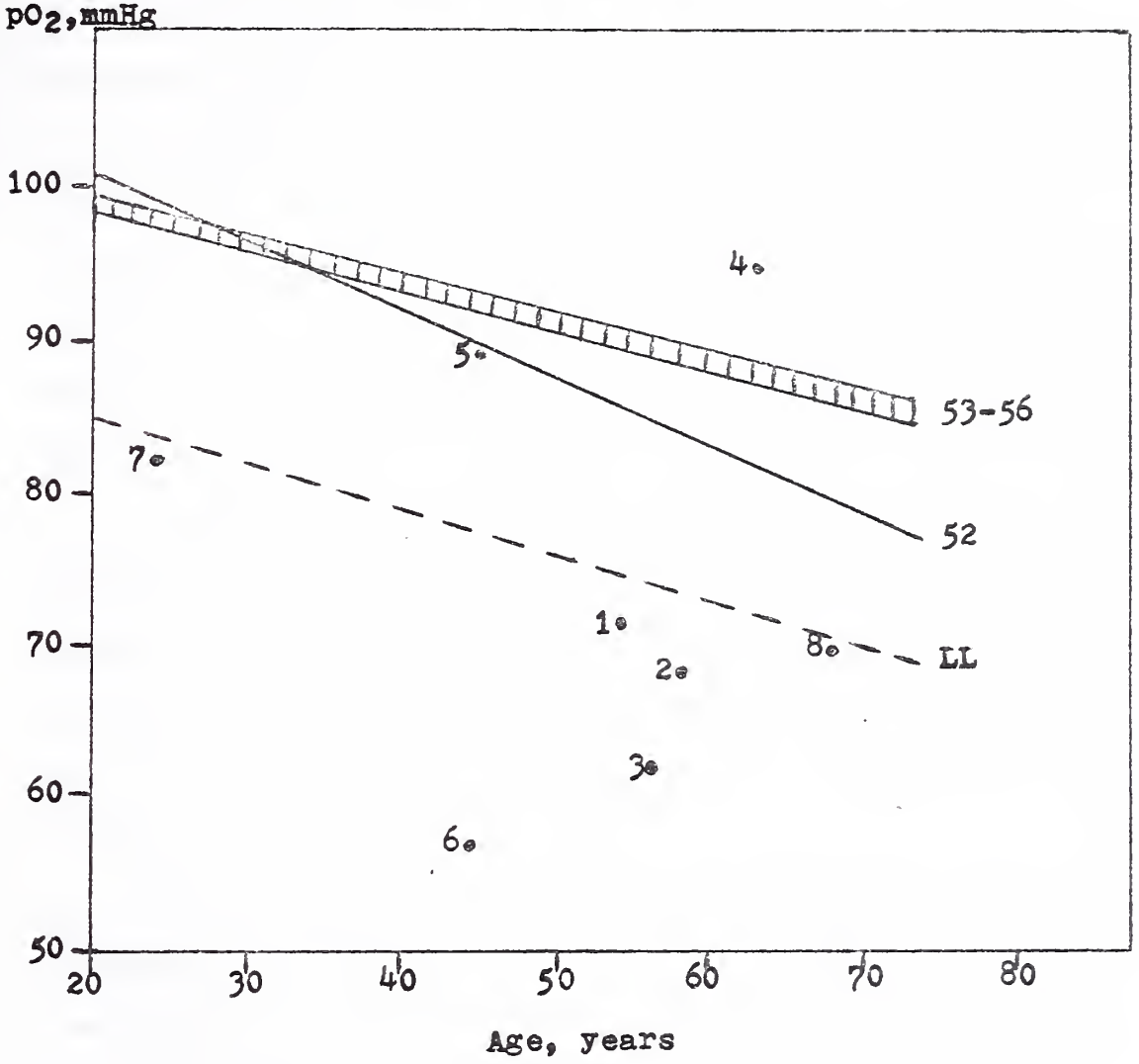
b	Pre-dialysis mean	$pCO_2 = 33$	$[HCO_3^-] = 20.6$
a	Post-dialysis mean	$pCO_2 = 31$	$[HCO_3^-] = 25.0$

Pre-dialysis measurements from two previous studies[17,28] are also shown in Figure 2. Both were dealing with milder degrees of acidosis before dialysis. The regression line found by Earnest et. al.[17] has a slightly lower slope (1.15) than found in this study (1.41), but their slope is within the 50% confidence level for the slope found in this study.

Dialysis in all three caused an increase in $[HCO_3^-]$ for the groups without significant increases in pCO_2. The slope of the regression line for the patients in this study was higher after dialysis but the difference was not significant ($t= 1.48, p=0.2$). In approximately one half of the post-dialysis measurements made, the pCO_2 and $[HCO_3^-]$ define a point lying within the significance band defined by Arbus et. al.[51] for acute respiratory alkalosis and the post-dialysis regression line parallels that band lying just to the left of it.

Figure 3 shows the mean arterial pO_2 before dialysis for each patient plotted against patient age and the regression lines for several studies in healthy subjects.[52-6] All studies showed a significant negative correlation of arterial pO_2 with age in "healthy" subjects with no differences in aveolar pO_2. No correlation of pCO_2 with age was found in these studies and the pCO_2 means reported were in the range of 40mmHg. One study eliminated smokers

Figure 3 - Change in Arterial pO_2 with Age



Past Studies - Normal Subjects - Regression Lines

52. Sorbini et.al.	pO_2 = 109. - 0.43(Age)	S.E.=±4.10
53. Conway et.al.	pO_2 = 102.5 - 0.22(Age)	S.E.=±4.70
54. Marshall et.al.	pO_2 = 104. - 0.25(Age)	
55. Mellemgaard	pO_2 = 104.2 - 0.27(Age)	
56. Raine&Bishop	pO_2 = 103.7 - 0.24(Age)	S.E.=±7.9

Note: Band includes lines 53-56

LL. Lower limit of normal from above studies (± 2 S.E.)

Present Study

Numbered Point = the mean pre-dialysis arterial pO_2 for patient number N

and studied lifelong residents of a rural area. Six of the eight patients have mean arterial pO_2 below the lowest 95% confidence levels reported.[56] As the subjects in this study are hyperventilating and presumably have higher aveolar pO_2 levels than the subjects of the studies cited, even greater abnormality in the aveolar-arterial difference in pO_2 is present than their depression in arterial pO_2 indicates.

Oxygen saturation ranged from 87 to 98% before dialysis and the mean for the group rose significantly, while the mean pO_2 was stable, reflecting the increase in the oxygen affinity of hemoglobin in blood of increased pH. The individual data for the values presented in Table 2 are in Appendix VI.

The possibility that the low arterial pO_2 demonstrated in the patients was driving respiration was investigated in seven patients by administering O_2. Appendix VII shows the data on individuals obtained before and after dialysis with O_2. In Table 3 mean changes with O_2 are compared to the mean changes with room air for the seven patients studied. Mid-dialysis measurements of pO_2 agree with post-dialysis values and the pO_2 on oxygen ranged from 126 to 339mmHg with O_2 saturations of at least 99%.

The patients as a group had the same pCO_2 and $[HCO_3^-]$

before dialysis on the control days as on the day they received O_2. The pH and pO_2 for the group were slightly higher on the O_2 day. Patient 3 had a high $[HCO_3^-]$ for him and it did not change by the end of dialysis although his pCO_2 did drop. The elevated $[HCO_3^-]$ was apparently the result of self-prescribed oral $NaHCO_3$. While O_2 administration raised the pO_2 of all patients, the changes in the three acid-base variables over dialysis were similar to those obtained on room air. Indeed,the pCO_2 showed less of an increase during dialysis with O_2 than with room air. Considering only those five patients with low pO_2, changes none of the conclusions above.

TABLE 3

	Pre		Post	Change	"t"test
pH-Room Air	7.38		7.48	0.10	- - - p<.001
Oxygen	7.40		7.50	0.10	
Difference	0.02	p>.10		0.00	
HCO_3^--Room Air	15.61		20.92	5.31	- - - p<.001
Oxygen	15.94		20.26	4.32	
Difference	0.33	p>.70		-0.99	p>.3
pCO_2-Room Air	27.64		28.97	1.33	- - - p<.05
Oxygen	26.79		26.93	0.14	
Difference	-0.85	p>.40		-1.19	p>.4
pO_2-Room Air	74.9		75.3	0.4	- - - p>.80
Oxygen	78.3		all>130	-	
Difference	3.4	p>.15			
Sat.-Room Air	94.0		95.2	1.2	- - - p<.01
Oxygen	94.6		99-100	-	
Difference	0.6	p>.40			

The low pO_2 levels in six of eight patients indicates a deficit in the oxygenation of the blood by the lungs. The change in the aveolar-arterial difference in pO_2 ($\Delta(A\text{-}a)DpO_2$) during dialysis estimates the effect, if any, of the procedure on the pulmonary dysfunction causing the increased aveolar-arterial difference. The mean $(A\text{-}a)DpO_2$ decreased slightly (1.6mmHg) but not significantly ($p>.5$). If the two patients with normal pO_2 are excluded the decrease in $(A\text{-}a)DpO_2$ is 3.5mmHg with a $p>.2$. Changes in the aveolar-arterial difference for pO_2 did not correlate with changes in pCO_2 during dialysis.

The precarious cardiovascular state of the patients has been previously outlined. During most of the dialysis periods measured the patients were free from rales or pulmonary symptoms of congestive failure. Patient 7 was an exception on two occasions coming to dialysis weighing 10 and 23% more than her lowest weight during the period of study. During both dialyses the pCO_2 rose and during one (23% overweight) the $(A\text{-}a)DpO_2$ decreased. Another patient(3) had clinical failure on one occasion and during dialysis showed the largest increase in pCO_2 (5.5mmHg) and decrease in $(A\text{-}a)DpO_2$ (33.6mmHg) recorded during the study. In the absence of gross failure the weight of the patient was taken as an index of possible pulmonary congestion. The per cent by which the pre-dialysis weight of the patients exceeded

their lowest recorded weight for the study period was calculated for each dialysis. No significant correlation exists between the per cent weight before dialysis and the change in pCO_2 or $(A-a)DpO_2$ during dialysis. The four dialyses done on three patients with pre-dialysis per cent excess weight of greater than 7% were all accompanied by an increase in pCO_2 at the end of dialysis. The twenty-four dialysis periods can be divided into groups during which ventilation (pCO_2) or lung function $(A-a)DpO_2$ changed. Table 4 shows the mean per cent excess weights before the dialyses during which the pCO_2 or $(A-a)DpO_2$ did change. The data for Table 4 are presented in Appendix VIII.

TABLE 4

	Dialyses	%Overweight	"t"test(weight)
$(A-a)DpO_2$			
increased	9	4.7	
decreased	9	7.0	$p>.30$
pCO_2			
increased	13	6.8	
decreased	6	3.6	$p>.10$

Only changes in $(A-a)DpO_2$ greater than o.5mmHg were included above.

When other measures of weight (e.g. weight change, % weight change, % excess weight after dialysis), other measures of lung function (simple pO_2), and other measures of ventilation ($pCO_2/[HCO_3^-]$) are compared, no correlations are demonstrated.

DISCUSSION

The patients all demonstrated a compensated metabolic acidosis before dialysis. In many instances the pCO_2 was maintained low enough to keep the pH in the normal range and, indeed, the best linear fit of the data is very nearly the line representing a constant pH of 7.40. The compensation (pCO_2 - $[HCO_3^-]$ ratio) demonstrated by this group is approximately the same as reported by Earnest et. al.[17] and Rosen et. al.[28] although the depression in $[HCO_3^-]$ observed in this study was greater than in theirs. The first study's patients had more frequent dialyses of longer duration while the second was done with acute renal failure patients who had received HCO_3^- therapy.

This study also confirms that chronic reductions in HCO_3^- concentration may occur without acidemia[17,28] in contrast to the conclusions of the studies that attempt to define a "significance band" for uncomplicated chronic metabolic acidosis. In this and the study of Earnest et. al.[17] "chronic" means three to four days of uremia. These patients seem to resemble the NH_4Cl loaded normals of Elkinton et. al.[8] more than the patients with metabolic acidosis studied by others. If the other investigators have included patients with neurologic disease or respiratory insufficiency, the difference is explained. If these three studies include many patients with congestive heart failure and additional hyperventilation on that basis, then the difference is explained. The actual

statistical significance of the observed differences cannot be formally evaluated. In any case the "significance band" for chronic metabolic acidosis has not been adequately established.

There is no reason to suppose that the patients in this study have less compensation for their acidosis than acid loaded normals, acute uremics, or diabetics as had been suggested by others.[18,20]

The study demonstrates significant increases in $[HCO_3^-]$ and pH during dialysis, a change found in essentially all of the dialyses investigated. No patient demonstrated a $[HCO_3^-]$ greater than 24mEq/l and almost all showed low $[HCO_3^-]$[37] at the end of dialysis. The mean pH is above normal[37] and all eight patients had an above normal pH following at least one dialysis with only five of twenty-four post-dialysis measurements being in the normal range. The group and individuals in it demonstrate the phenomenon of a respiratory alkalosis developing during repair of a HCO_3^- deficit.

No direct measure of ventilation was made in this study. Instead the assumptions are made that before and after dialysis CO_2 production is constant and given rates of ventilation remove CO_2 at the same rates. To the unknown extent that these assumptions are valid, changes in arterial pCO_2 inversely reflect changes in mean aveolar ventilation. Earnest et. al.[17] report that in six patients studied ventilation varied slightly in both directions during dialysis and that small changes in

arterial pCO_2 in the appropriate direction accompany the variations in ventilation.

The arterial pCO_2 and presumably the mean aveolar ventilation did not change consistently during dialysis. The changes were small (ranging from -4 to +5.5 mmHg) and variable in direction for most of the patients. The two patients(1 and 8) whose variation was consistent in direction for all three dialysis runs consistently changed in opposite directions. At least 50% of the reported pCO_2 changes are so small(less than 1.5 mmHg) that they are probably within the error of the calculated pCO_2 itself. The statistical significance of the mean change in pCO_2 is doubtful unless patient 8 with non-medullary neurologic disease is eliminated. The study confirms that pCO_2 tends not to change in many instances where alkalemia is developing and does have significant implications for the theory of Mitchell et. al.[26]

The previously unreported finding of low pO_2 levels in six of the eight patients studied complicates the interpretation of the data above in two ways. The chronically decreased pO_2 by itself may be maintaining ventilation at an increased level above the level caused by acidosis. The low pO_2, even if not an effective respiratory stimulant, may indicate the presence of a cardio-pulmonary disorder which is causing hyperventilation.

There is some debate about the level of arterial pO_2 at which O_2 drive is significant in the absence of CO_2 retention.

The generally accepted statement is that arterial pO_2 must decrease below 50-60 mmHg in normal humans before significant increases in ventilation regularly occur.[57] Small changes occur in acute studies in more than half of normals at arterial pO_2 levels of 80-85 mmHg. The increases ranged up to 20% of control.[58] Others have noted that while long term O_2 administration has no effect, single breaths of O_2 cause transient decreases in ventilation in animals and man when pO_2 is normal. The response in animals requires intact nerves from the carotid and aortic bodies. Acidosis increases the response of the carotid body to acute O_2 lack in animals.

In all patients given O_2 during dialysis the pO_2 went above 125mmHg, a level which should abolish most if not all of the respiratory drive secondary to low pO_2. The administration of O_2 during dialysis did not influence significantly the previously demonstrated changes in pH, $[HCO_3^-]$, and pCO_2 during dialysis. If anything, there was less tendency for the pCO_2 to increase during dialysis and this is true if patient 3, whose $[HCO_3^-]$ was originally high and did not increase, is eliminated. If chronically hypoxic patients are comparable to acclimatized normals, O_2 administration would not be expected to cause dramatic decreases in ventilation.[36] But some change in ventilation would be expected by Mitchell et. al.[26] when at the end of dialysis both hypoxic and acidotic stimulation of peripheral receptors is much decreased.

The mean increase in $[HCO_3^-]$ of the group during dialysis with O_2 was almost 1 mEq/l less than during dialysis with room air. This difference is due entirely to the unchanged $[HCO_3^-]$ of patient 3. The mean change with O_2 when patient 3 is excluded is 5.2mEq/l, exactly the mean change on room air. The increased oxygen saturation of the patients when on O_2 can be expected to decrease the $[HCO_3^-]$ by no more than 0.5 mEq/l, a Haldane Effect too small to be demonstrated in this study.[1]

The finding of significantly decreased pO_2 and presumably even more severely increased alveolar-arterial pO_2 differences probably indicates pulmonary dysfunction. The patients are anemic and this can cause slightly increased $(A-a)DpO_2$[60] and lowered arterial pO_2 without apparent pulmonary disease. The changes were small (maximum of 5mmHg in pO_2) and the only evidence of normal lung function was normal spirometry in the nine patients.[60] Acute anemia in dogs causes no change in the gradient or arterial pO_2.[61] Most of the sampling in this study was done with the patients sitting to some degree which, if anything, tends to increase arterial pO_2.[56] All patients except patient 8 were ambulatory to varying degrees and were not on the type of absolute bed rest which lowered the arterial pO_2 of young athletes after 10 days by an average of 9mmHg.[62]

Uremia without some complicating pulmonary disorder has not been reported to increase $(A-a)Dp0_2$ in the past twenty years reviewed. Dialysis itself has no reported effect on $p0_2$ other than the measurable increase in the $p0_2$ of blood leaving the dialysis coil when the entering blood has low $p0_2$.[63] Extracorporeal circulation may cause recognizable complications (e.g. embolism) leading to decreased arterial $p0_2$ but no reports of low $p0_2$ without complications appear.

All of the patients who had decreased $p0_2$ also had a past history of congestive heart failure and pulmonary edema. Indeed, in patient 7, who had changes on chest films and accumulated large amounts of excess weight between dialyses, no other cause for low $p0_2$ need be sought. The other five regularly were without clinical indications of pulmonary congestion and had unremarkable lungs by X-ray in the period of the study.

During dialysis the group as a whole showed no improvement in lung function as estimated from their $p0_2$ or $(A-a)Dp0_2$. This was true if only those with predialysis low $p0_2$ were considered. Of the three occasions in two patients when pulmonary congestion was present clinically, improvement over dialysis in $(A-a)Dp0_2$ and arterial $p0_2$ was found twice. In the absence of direct evidence of pulmonary congestion or cardiac function,

the per cent excess weight present was used to indicate the relative amount of excess fluid present. This measure is at best weakly correlated with degrees of pulmonary congestion or heart failure but was the only datum available. While the mean % excess weight was greater numerically for the patients whose $(A-a)Dp_{O_2}$ improved during dialysis, the difference is not statistically significant and is due almost entirely to the inclusion of the astoundingly high weight(23% excess) of patient 7 on one occasion. If the low p_{O_2} in the five patients is the result of congestion in the lungs, then dialysis does not appear to correct the disorder enough to correct the p_{O_2}. Whatever the cause of the low p_{O_2}, it is not corrected by dialysis.

The other possible cause of low p_{O_2} in these five patients in the presence of normal lungs on X-ray and low arterial p_{CO_2} is pulmonary embolism.[1] No past documented episode of embolism had occurred in these patients. Some instances of unexplained dyspnea and tachypnea of acute onset had been noted by observers[64], but evaluation of such episodes is difficult in these generally anxious, acidotic, ill patients. Apparently "clotted" shunt veins have been known to "open up" spontaneously.[64] Symptomatic pulmonary embolism from the shunts of dialysis patients has been reported.[65]

The two patients with normal p_{O_2} were also the two patients who had been on hemodialysis the least amount of time(4 months).

One of these was also the only patient without a past history of congestive heart failure.

Single arterial samples were obtained from five patients with uremia who had received either no hemodialysis or in one case, only three treatments. Two were clinically in failure and had low pO_2. Two had past histories of pulmonary edema, but had normal pO_2 (over 90mmHg) at the time of measurement. One had no history of failure and a normal pO_2. These data are difficult to interpret because patients never requiring dialysis are different from those who do in many other ways. In any case, no unexplained low pO_2 levels were found in this group of uremics with little hemodialysis exposure.

The syndrome of multiple small pulmonary emboli is non-specific symptomatically, dyspnea on exertion being the universal complaint. The patients have pO_2 levels from normal to low. Hyperventilation at rest is not seen unless there is an acute episode or the disease is far advanced.[66] In patients on hemodialysis regularly subjected to manipulation of their blood clotting mechanisms, long periods of bed rest, extracorporeal circulation, and frequent trauma to veins, some embolization has undoubtedly occurred. The presence of a significant loss of pulmonary vascular bed can be established by analyzing the arterial - end aveolar gradient for pCO_2. If pCO_2 in the end aveolar air is more than 5mmHg below arterial pCO_2, presumably because of mixing of air from aveoli without blood flow,

then pulmonary vascular occlusion is likely. This test presumes no other cause of uneven ventilation and perfusion is present, especially chronic obstructive pulmonary disease. Left heart failure does not cause false positive results in the absence of gross X-ray changes.[67] The finding of a difference of less than 5mmHg would eliminate this syndrome as a possible explanation for the low pO_2 demonstrated in five patients during this study.

Using this group of patients in an attempt to test the theory of Mitchell et. al.[26] is complicated by the history of congestive failure in seven and the presence of pulmonary dysfunction in six of the eight patients. It is probable that some congestive failure was present in the patients studied previously.[17,28] If the pulmonary disorder is not corrected by dialysis and is causing hyperventilation, then the lack of a pCO_2 increase does not contradict the theory. If the disorder is not causing hyperventilation, the lack of a pCO_2 increase does contradict the theory.

As indicated, if $(A-a)DpO_2$ is taken as the measure, then the pulmonary disorder is not improved by dialysis. The change in pCO_2 did not correlate with changes in $(A-a)DpO_2$. The maximum increase in pCO_2 reported was observed in a patient with obvious pulmonary congestion at the time and whose lung function improved as indicated by a decrease in $(A-a)DpO_2$. But increases in pCO_2 of 4mmHg occurred three times, always in

patients whose (A-a)DpO_2 indicated unchanged or poorer lung function after dialysis. No strong correlation existed between the change in pCO_2 and the amount of excess fluid as estimated from the % excess weight before dialysis. As noted, the six highest excess weights recorded occurred before dialyses that were accompanied by increases in pCO_2. The mean excess weight also tended to be higher when pCO_2 rose but not significantly so.

Within the limits of the indirect data available it appears that the group in general shows no improvement in their respiratory disorder during dialysis. When improvement is probable, the change in ventilation is inconsistent in direction, suggesting that the disorder does not cause important hyperventilation. The presence of congestive failure clinically or implied by weight was often associated with increases in pCO_2 during dialysis. In these circumstances the increase in pCO_2 and decrease in ventilation may have been caused by the improvement in heart failure during dialysis and not changes in the acid-base status of the blood or CSF. This study, at least, offers no evidence to support the theory of Mitchell et. al.

The study of one normal subject by Mitchell and Singer[68] during the correction of metabolic acidosis demonstrates the changes they predict in the blood, ventilation, and CSF. Enough HCO_3^- was rapidly administered to the subject to acutely raise his plasma concentration above normal and his blood pCO_2 did increase. Given the arterial pCO_2 increase, the CSF acidosis

followed and was associated with continued hyperventilation. The critical problem for the hypothesis, however, is to demonstrate that the rise in pCO_2 required usually takes place. In this and other studies outlined the rise did not take place. It is difficult to propose an increased arterial-CSF gradient for pCO_2 leading to a CSF acidosis without changes in blood pCO_2 in the absence of experimental evidence of such changes. It is possible, but difficult to test, that the required rise in arterial pCO_2 is so small that the error of measurement prevents its detection.

In contrast to the other investigations cited Fencil, Miller, and Pappenheimer[69] using unanesthetized goats reported that cisternal and ventricular CSF pH was proportional to the blood $[HCO_3^-]$ during chronic metabolic acidosis or alkalosis. The CSF pH variation was small but seemed to account for the changes in ventilation observed. They concluded that the ventilatory response to metabolic acidosis and alkalosis, CO_2 inhalation, and CSF infusion with solutions of varying pH could be entirely explained by the change in interstitial pH near the blood-brain barrier. Peripheral chemoreceptors were not important in controlling ventilation in the conditions studied. Although no data were obtained, their model postulates that persistent hyperventilation following correction of metabolic acidosis results from the impermeability of the blood-brain barrier to HCO_3^-. The data from this study are consistent with their formulation.

Evaluation of theories of respiratory control using patients with uremia will almost always be complicated by the problems in this study. Diabetics, acid loaded normals, and patients with diarrheal acidosis are probably more suitable subjects for study but controlled conditions of treatment are more difficult to obtain in these rapidly corrected acidoses. The system outlined by Chazan et. al.[29] for dogs is probably the most reasonable way of investigating respiratory control. Administration of HCO_3^- in reasonable amounts followed by the appropriate measurements on the acidotic dogs should provide some of the missing facts.

The clinical significance of the respiratory alkalosis regularly produced by dialysis is doubtful as it is usually mild (less than 7.61) and is self-correcting. The seizures and other manifestations of the "dis-equilibrium syndrome" are probably secondary to osmotic shifts, not alkalosis, and may even be aggravated by increasing pCO_2.[28,70] Tetany was not observed in these patients. If tetany does occur during dialysis, one can be fairly sure that respiratory alkalosis is playing some role in its appearance. The significance of the low pO_2 depends on its etiology.

Appendix I- Patient Data

Patient-Unit#	Exp#	Sex	Age	Dialysis Total	Dialysis Hemo	Disease
G.L. 56-60-22	1	M	54	2yr.	8mo.	Renal TB
J.P. 02-85-67	2	M	58	1½	8	End stage biopsy
H.M. 05-89-30	3	M	56	2	16	End stage biopsy
E.L. 68-10-41	4*	M	63	½	4	Chronic pyelo-nephritis
V.K. 72-08-74	5	F	45	5mo.	5	Polycystic kidneys
B.K. 72-86-57	6	F	44	1yr.	7	Chr. glomerulo-nephritis
V.B. 70-57-40	7	F	24	2	16	Chr. glomerulo-nephritis
M.S. 73-53-24	8*	M	68	1½	6	End stage biopsy

*These two patients had radial artery to autologous saphenous vein graft to brachial vein shunts. All others had direct radial artery to anti-brachial vein shunts.

Appendix II- Dialysis Apparatus and Fluid Specifications

Travenol Artificial Kidney
" Twin Kolff Type Coils with Cuprophan Membrane

Priming- Start 500-700cc of normal saline to fill tubing and coil
End Blood flushed from coil and tubing to patient with 200cc normal saline

Dialysis Bath

3432ml of Travenol Dialysis Salt Concentrate in 120 liters of tap water

Nominal Concentrations

Na^+	127.	mEq/l	
Ca^{++}	3.1	"	
Mg^{++}	1.3	"	
K^+	2.2	"	increased with KCl as necessary
CH_3COO^-	36.3	mEq/l	
Cl^-	97.	"	

Glucose 234 mg/100ml

Measured Osmolarity

280-290mOsm/l

Appendix III- Comparison of Measured and Derived CO_2 Content

Sample #	pH units	pCO_2 mmHg	CO_2-nomo. mM/l	CO_2-meas. mM/l	Difference mM/l
1	7.49	33.0	25.5	21.1	4.4
2	7.50	26.5	20.7	19.4	1.3
3	7.33	29.0	15.4	16.3	-0.9
4	7.35	38.5	21.5	20.1	1.4
5	7.39	34.5	21.3	18.7	2.6
6	7.33	34.5	18.5	17.4	1.1
7	7.42	24.0	15.5	12.0	3.5
8	7.37	24.0	14.0	12.1	1.9
9	7.40	34.0	21.3	19.8	1.5
10	7.36	38.5	22.0	18.7	3.3
11	7.26	38.5	17.5	16.1	1.4
12	7.38	35.0	20.8	18.2	2.6
13	7.46	32.5	23.5	24.4	-0.9
14	7.34	38.5	20.1	18.2	1.9
15	7.42	33.0	21.8	21.9	-0.1
16	7.43	32.0	21.3	20.4	0.9
17	7.46	38.5	27.6	25.0	2.6
18	7.40	33.5	21.1	19.6	1.5
19	7.45	33.5	23.5	22.8	0.7
20	7.34	30.5	16.6	14.6	2.0
21	7.42	22.5	14.6	12.7	1.9
22	7.46	34.5	24.6	21.9	2.7
23	7.43	29.5	19.6	17.0	2.6
24	7.49	32.5	25.1	21.4	3.7
25	7.37	35.0	20.3	16.7	3.6
26	7.46	37.5	26.8	21.7	5.1

Mean Difference ± 2.0
S.D. ± 1.50
Difference > 0 with "t" $> 7.$
$p < 0.01$

pH and pCO_2 - measured

CO_2-nomo. - read from nomogram using measured pH and pCO_2

CO_2-meas. - CO_2 content of plasma by Van Slyke manometric technique

Difference = (CO_2-nomo.) - (CO_2-meas.)

Appendix IV- Derivation of Estimate of $\Delta(A\text{-}a)Dp_{O_2}$

The equation for mean aveolar pO_2:[1]

$$P_{A_{O_2}} = F_{I_{O_2}} (P_B - P_{H_2O}) - P_{A_{CO_2}} \left[F_{I_{O_2}} + \left[\frac{(1-F_{I_{O_2}})}{R} \right] \right]$$

where $P_{A_{O_2}}$ = mean aveolar pO_2

$F_{I_{O_2}}$ = fraction of O_2 in inspired air

$P_{A_{CO_2}}$ = mean aveolar pCO_2=arterial pCO_2($P_{a_{CO_2}}$) by assumption

P_B = barometric pressure

P_{H_2O} = water vapour pressure at body temperature

R = respiratory quotient

The change from pre(1) to post(2) dialysis measurement, assuming that $F_{I_{O_2}}$, P_B, P_{H_2O}, and R do not change is:

$$P_{A_{O_2}}(2)-P_{A_{O_2}}(1) = \left[P_{a_{CO_2}}(1)-P_{a_{CO_2}}(2) \right] \left[F_{I_{O_2}} + \frac{(1-F_{I_{O_2}})}{R} \right]$$

The last term resolves to 1.2 if $F_{I_{O_2}}$= 0.209 and R= 0.8:

$$P_{A_{O_2}}(2)-P_{A_{O_2}}(1) = 1.2 \left[P_{a_{CO_2}}(1)-P_{a_{CO_2}}(2) \right] \qquad \#1$$

By definition:

$$\Delta(A\text{-}a)Dp_{O_2} = \left[P_{A_{O_2}}(2)-P_{a_{O_2}}(2) \right] - \left[P_{A_{O_2}}(1)-P_{a_{O_2}}(1) \right] \qquad \#2$$

where $P_{a_{O_2}}$ = arterial pO_2

Substituting #1 into #2:

$$\Delta(A\text{-}a)Dp_{O_2} = \left[P_{a_{O_2}}(1)-P_{a_{O_2}}(2) \right] + 1.2 \left[P_{a_{CO_2}}(1)-P_{a_{CO_2}}(2) \right]$$

or $$\Delta(A\text{-}a)Dp_{O_2} = -\left[\Delta P_{a_{O_2}} + 1.2(\Delta P_{a_{CO_2}}) \right]$$

where:

$\Delta P_{a_{O_2}} = P_{a_{O_2}}(2)-P_{a_{O_2}}(1)$ = change in arterial pO_2

$\Delta P_{a_{CO_2}} = P_{a_{CO_2}}(2)-P_{a_{CO_2}}(1)$ = change in arterial pCO_2

Appendix V- Weight, Hematocrit, and Electrolytes

Patient	Pre-dialysis					Post-dialysis				
	Weight lbs.	Hct. %	Na^+ mEq/liter	Cl^- mEq/liter	K^+ mEq/liter	Weight lbs.	Hct. %	Na^+ mEq/liter	Cl^- mEq/liter	K^+ mEq/liter
1	142.75	15½	135	95	6.8	136.	16	136	95	4.8
	141.75	13½	134	94	6.2	138.5	18½	134	91	3.9
	145.75	15½	134	95	6.3	140.75	19	139	97	4.4
2	162.5	18	142	101	6.3	160.75	17½	140	96	3.7
	163.75	17½	140	99	7.1	159.25	18	137	94	3.4
	164.	19	143	102	6.5	161.	21	140	100	3.8
3	138.	15½	136	100	6.2	134.	20½	129	101	4.8
	134.	20½	133	91	7.0	130.5	19½	137	94	4.1
	139.	16½	138	94	5.4	134.5	21	135	93	3.4
4	118.5	21½	135	108	4.5	116.25	19½	136	100	3.2
	119.25	20½	133	101	3.9	115.25	19½	135	94	3.2
	120.25	21½	136	106	5.3	117.5	20½	132	102	3.5
5	136.	17½	138	101	5.4	132.75	17	142	99	3.6
	137.5	17	143	101	5.8	135.25	16	129	99	3.9
	140.	16	142	106	5.9	137.5	18½	135	96	4.0
6	152.5	17½	132	100	6.6	146.25	17	133	95	3.7
	150.	16½	134	95	6.0	145.25	18½	121	90	3.5
	145.25	16½	128	92	6.0	141.	15½	132	93	3.6
7	123.25	23½	132	86	5.9	116.	21½	135	89	3.3
	117.25	24	130	92	4.9	112.	22½	124	93	3.0
	138.5	21	145	106	4.4	132.	20½	136	100	4.2
8	-	19½	133	92	5.8	-	22½	134	92	4.2
	-	20	138	100	5.1	-	22½	130	94	3.8
	-	18½	138	100	6.2	-	23½	135	104	3.9

Appendix VI- Arterial Acid-Base, pO_2 and O_2 Saturation

Patient	Pre-dialysis					Post-dialysis				
	pH	pCO_2	HCO_3^-	pO_2	Sat.	pH	pCO_2	HCO_3^-	pO_2	Sat.
1.	7.38	30½	17.2	72	93	7.46	34	23.4	78	95
	7.37	30½	16.7	70	93	7.44	33½	22.2	65	93
	7.43	25	16.0	72	94	7.49	27½	20.5	60	92
2.	7.34	35	17.1	59	88	7.42	33½	20.9	79	95
	7.31	33	15.8	70	93	7.45	32½	21.9	69	94
	7.37	28½	15.8	76	94	7.46	30	20.9	80	96
3.	7.43	29	18.5	54	88	7.46	34½	23.9	81	96
	7.31	32	15.3	68	93	7.47	31½	22.2	76	96
	7.37	32	17.8	63	91	7.46	33	22.8	69	94
4.	7.40	31½	18.6	89	97	7.45	32½	21.8	88	97
	7.40	28½	17.1	94	97	7.48	28½	20.8	91	97
	7.35	26½	13.9	101	97	7.49	25	18.4	91	97
5.	7.34	26½	13.7	91	97	7.47	30½	21.6	86	97
	7.40	28	16.6	89	97	7.43	32	20.6	64	93
	7.37	27½	15.3	88	96	7.52	26½	21.0	89	98
6.	7.42	19½	12.1	53	87	7.56	23	20.1	54	92
	7.40	26	15.6	55	89	7.50	27	20.3	65	94
	7.45	24½	16.5	63	93	7.52	24½	19.3	55	92
7.	7.36	23	12.4	88	97	7.50	27	20.6	78	97
	7.40	22	12.7	75	94	7.61	18	17.6	74	97
	7.41	21½	13.0	83	96	7.50	24	18.4	91	98
8.	7.46	30½	21.0	67	93	7.48	29	21.1	74	95
	7.41	28½	17.4	75	94	7.51	26	20.0	71	95
	7.44	29½	19.2	68	93	7.53	26½	21.3	68	94

pH, units - measured
pCO_2, mmHg - from nomogram using pH and CO_2 content
HCO_3^-, mEq/l - calculated per text using pCO_2 and CO_2 content

pO_2, mmHg - measured
O_2 Sat., % - from nomogram using temperature, pH, and pO_2

Appendix VII- Acid-Base and pO_2 during Oxygen Administration

Patient -Time	pH units	$[H^+]$ nM/l	$[HCO_3^-]$ mEq/l	pCO_2 mmHg	pO_2 mmHg	Sat. %
1 -Pre	7.38	41.7	14.9	26	81	95
-Mid	7.44	36.4	18.3	28	136	99
-Post	7.48	33.1	20.3	28	140	99
2 -Pre	7.36	43.7	15.8	29½	76	94
-Mid	7.41	38.9	15.1	25	132	99
-Post	7.48	33.1	18.7	26	136	99
3 -Pre	7.42	38.0	20.6	33	60	90
-Mid	7.50	31.6	21.1	28	326	100
-Post	7.53	29.5	20.4	25½	339	100
4 -Pre	7.37	42.7	13.2	24	90	96
-Mid						
-Post	7.48	33.1	19.5	27	227	100
5 -Pre	7.36	43.7	14.9	27½	90	96
-Mid	7.40	39.8	17.4	29	126	99
-Post	7.48	33.1	22.2	31	142	99
6 -Pre	7.49	32.4	16.2	22	70	95
-Mid						
-Post	7.56	27.5	20.6	24	159	99
7 -Pre	7.42	38.0	16.0	25½	81	96
-Mid	7.45	35.5	18.5	27½	151	99
-Post	7.49	32.4	20.1	27	147	99

Pre - before dialysis or oxygen begun.
Mid - 2½ to 3 hours after dialysis and O_2 begun.
Post- 5 hours after dialysis and O_2 begun.

Data obtained in same manner as for Appendix VI.
$[H^+] = \frac{1}{10^{pH}} \times 10^2$, nanaMoles per liter

Appendix VIII- Pre-dialysis % Excess Weight and the Change in (A-a)DpO_2 and Arterial pCO_2 and pO_2

Patient #	pCO_2 change mmHg	pO_2 change mmHg	Δ(A-a)DpO_2 mmHg	%excess wt. lbs.
1	3.5	6	-10.2	4.9
	3.	- 5	1.4	4.2
	2.5	-12	9.0	7.2
2	-1.5	20	-18.2	2.0
	-0.5	- 1	1.6	2.7
	1.5	4	- 5.8	3.0
3	5.5	27	-33.6	5.7
	-0.5	8	- 7.4	2.7
	1.	6	- 7.2	6.5
4	1.	- 1	- 0.2	2.6
	0.	- 3	3.0	3.2
	-1.5	-10	11.8	4.1
5	4.	- 5	0.2	2.4
	4.	-25	20.2	3.6
	-1.	1	0.2	5.5
6	3.5	1	- 5.2	8.2
	1.	10	-11.2	6.4
	0.	- 8	8.0	3.2
7	4.	-10	5.2	10.0
	-4.	- 1	5.8	4.7
	2.5	8	-11.0	23.2
8	-1.5	7	- 5.2	-
	-2.5	- 4	7.0	-
	-3.	0	3.6	-

All changes are derived from post-dialysis value minus pre-dialysis value calculations so that increases during dialysis are positive.

REFERENCES

1. Comroe JH: Physiology of Respiration. Chicago, Year Book Medical Publishers, Inc., 1965

2. Pitts RF: Physiology of the Kidney and Body Fluids. Chicago, Year Book Medical Publishers, Inc., 1966

3. Elkinton JR: Hydrogen ion transfer in health and disease. Annals of Internal Medicine 57:660-681, 1962

4. Gambino SR: General discussion. Annals of the New York Academy of Science 133:235-243, 1966

5. Moller B: Hydrogen ion concentration in arterial blood-a clinical study of patients with diabetes and diseases of the kidneys, lungs and heart. Acta Medica Scandinavica 163(Supp. 348):1-238, 1959

6. Lennon EJ, Lemann JL: Defense of hydrogen ion concentration in chronic metabolic acidosis. Annals of Internal Medicine 65:265-274, 1966

7. Albert MS, Dell RB, Winters RW: Quantitative displacement of acid-base equilibrium in metabolic acidosis. Annals of Internal Medicine 66:312-322, 1967

8. Elkinton JR, Huth EJ, Webster GD, et al: Renal excretion of hydrogen ion in renal tubular acidosis: I. Quantitative assessment of the response to ammonium chloride as an acid load. American Journal of Medicine 29:554-570, 1960

9. Elkinton JR: Clinical disorders of acid-base regulation. Medical Clinics of North America 50:1325-1350, 1966

10. Peters JP: The response of the respiratory mechanism to rapid changes in the reaction of the blood. American Journal of Physiology 44:84-108, 1917

11. Winters RW, Lowden JA, Ordway NK: Observations of carbon dioxide tension during recovery from metabolic acidosis. Journal of Clinical Investigation 37:640-645, 1958

12. Singer RB, Clark JK, Barker ES, et al: The acute effects in man of rapid intravenous infusion of hypertonic sodium bicarbonate solution. Medicine 34:51-95, 1955

13. Weller JM, Swan RC, Merrill JP: Change in the acid-base balance of uremic patients during hemodialysis. Journal of Clinical Investigation 32:729-735, 1953

14. Sanchez SL: Acid-base equilibrium in patients with chronic renal failure in whom life is sustained by periodic hemodialysis. Clevland Clinical Quarterly 31:127-139, April, 1964

15. Pauli HG, Vorburger C, Reubi F: Chronic derangement of cerebrospinal fluid acid-base components in man. Journal of Applied Physiology 17:993-998, 1962

16. Cowie J, Lambie AT, Robson JS: The influence of extracorporeal dialysis on the acid-base composition of blood and cerebrospinal fluid. Clinical Science 23:397-404, 1964

17. Earnest DL, Sadler JM, Ingram RH, et al: Acid-base balance in chronic hemodialysis. Transactions. American Society for Artificial Internal Organs 14:434-437, 1968

18. Henderson LW, Rodriguez B, Hyde RW, et al: Respiratory compensation in metabolic acidosis. Clinical Research 14: 366, 1966

19. Alexander JK, West JR, Wood JA, et al: Analysis of the respiratory response to carbon dioxide inhalation in varying clinical states of hypercapnia, anoxia, and acid-base derangement. Journal of Clinical Investigation 34:511-532, 1955

20. Pauli HG, Reubi F: Respiratory control in uremic acidosis. Journal of Applied Physiology 18:717-721, 1963

21. Winterstein H: Chemical control of pulmonary ventilation: III. The reaction theory of respiratory control. New England Journal of Medicine 255:331-337, 1956

22. Mitchell RA, Loeschike HH, Severinghaus JW, et al: Regions of respiratory chemosensitivity on the surface of the medulla. Annals of the New York Academy of Science 109: 661-681, 1963

23. Bradley RD, Semple SJG: A comparison of certain acid-base characteristics of arterial blood, jugular venous blood, and cerebrospinal fluid in man and the effect on them of some acute and chronic acid-base disturbances. Journal of Physiology (London) 160:381-391, 1962

24. Posner JB, Swansen AG, Plum F: Acid-base balance in cerebrospinal fluid. Archives of Neurology 12:479-496, 1965

25. Agrest A, Roehr EE: Relacion electrolitica y acido-basica entre sangre arterial y liquido cefalorraquideo en trasternos del equilibrio acido-basica. Medicina 23:173-187, 1963

26. Mitchell RA, Carmen CT, Severinghaus JW, et al: Stability of cerebrospinal fluid pH in chronic acid-base disturbances in blood. Journal of Applied Physiology 20:443-452, 1965

27. Schwab M: Das Saüre-Base Gleichgewicht im Arteriellen Blut und Liquor cerebrospinalis bei chronishen Niereninsuffizienz. Klinische Wochenschrift 40:765-772, 1962

28. Rosen SM, O'Connor K, Shaldon S: Hemodialysis disequilibrium. British Medical Journal 2:672-675, 1964

29. Chazan JA, Appleton FM, London AM, et al: Effects of chronic metabolic acid-base disturbances on the composition of cerebrospinal fluid in the dog. Clinical Science 36: 345-358, 1969

30. Gesell R, Hertzman AB: Regulation of respiration. American Journal of Physiology 78:610-629, 1926

31. Robin ED, Whaley RD, Crump CH, et al: Acid-base relations between spinal fluid and arterial blood with special reference to control of ventilation. Journal of Applied Physiology 13:385-392, 1958

32. Posner JB, Plum F: Protection of CSF pH and brain function during severe metabolic acidosis. Transactions. American Neurological Society 92: 38-43, 1966

33. Manfredi F: Acid-base relations between serum and cerebrospinal fluid in man under normal and abnormal conditions. Journal of Laboratory and Clinical Medicine 59:128-136, 1962

34. Fisher VJ, Christiansen LC: CSF acid-base balance during a changing ventilatory state in man. Journal of Applied Physiology 18:712-716, 1963

35. Albert MS, Rahill WJ, Vega L, et al: Acid-base changes in cerebrospinal fluid of infants with metabolic acidosis. New England Journal of Medicine 274:719-721, 1966

36. Severinghaus JW, Mitchell RA, Richardson BW, et al: Respiratory control at high altitude suggesting active transport regulation of CSF pH. Journal of Applied Physiology 18:1155-1166, 1963

37. The ad hoc committee report on methodology. Annals of the New York Academy of Science 133:259-267, 1966

38. Instruction Handbook:Model 113-S2 pH/Blood Gas Analyzer. Lexington, Mass., Instrumentation Laboratory, Inc., 1968

39. Rosenthal TB: The effect of temperature on the pH of blood and plasma in vitro. Journal of Biological Chemistry 173:25-28, 1948

40. Severinghaus JW, Stupfel M, Bradley AF: Accuracy of blood pH and pCO_2 determinations. Journal of Applied Physiology 9:189-196, 1956

41. Bradley AF, Stupfel M, Severinghaus JW: Effect of temperature on pCO_2 and pO_2 of blood in vitro. Journal of Applied Physiology 9:201-204, 1956

42. Torres GE: Validation of oxygen electrode for blood. Journal of Applied Physiology 18:1008-1013, 1963

43. Eldridge F, Fretwell IK: Change in oxygen tension of shed blood at various temperatures. Journal of Applied Physiology 20:790-792, 1965

44. Peters JP, Van Slyke DD: Quantitative Clinical Chemistry-II. Baltimore, Williams and Wilkins, 1932

45. Directions for Use for the Van Slyke - Neill Manometric Gas Analysis Apparatus. Philadelphia, Arthur H. Thomas Co.,1958

46. Astrup P: A simple electrometric technique for determination of CO_2 tension in blood and plasma, total content of carbon dioxide in plasma, and bicarbonate content in 'separated' plasma at a fixed carbon dioxide tension (40 mmHg). Scandinavian Journal of Clinical Investigation 8:33-43, 1956

47. Austin JM, Willen GE, Hastings AB, et al: Studies of gas and electrolyte equilibria in blood. Journal of Biological Chemistry 54:121-147, 1922

48. Brooks D, Wynn V: Use of venous blood for pH and pCO_2 studies. Lancet 1:22-30, 1959

49. Siggard-Andersen O: Blood acid-base alignment nomogram. Scandinavian Journal of Laboratory and Clinical Investigation 15:211-217, 1963

50. Hardy RJ, Assistant Professor of Public Health(Biometry): Private communication

51. Arbus GS, Herbert LA, Levesque PR, et al: Characterization and clinical application of the 'significance band' for acute respiratory alkalosis. New England Journal of Medicine 280:117-123, 1969

52. Sorbini CA, Grassi V, Solinas E, et al: Arterial oxygen tension in relation to age in healthy subjects. Respiration 25:3-13, 1968

53. Conway CM, Payne JP, Tomlin PJ: Arterial oxygen tension of patients awaiting surgery. British Journal of Anaesthesiology 37:405-409, 1965

54. Marshall BE, Miller RA: Some factors influencing post-operative hypoxemia. Anaesthesiology 20:408-428, 1965

55. Mellemgaard K: The aveolar-arterial oxygen difference: it's size and components in normal man. Acta Physiologica Scandinavica 67:10-20, 1966

56. Raine JM, Bishop JM: A-a difference in O_2 tension and physiological dead space in normal man. Journal of Applied Physiology 18:284-288, 1963

57. Hornbein TF: The chemical regulation of ventilation, Physiology and Biophysics. Edited by Ruch, Patten. Philadelphia, WB Saunders Co., 1965, pp 803-819

58. Dripps RD, Comroe JH: The effect of the inhalation of high and low oxygen concentrations on respiration, pulse rate, ballistocardiogram and arterial oxygen saturation(oximeter) of normal individuals. American Journal of Physiology 149:227-291, 1947

59. Dejours P: Control of respiration by arterial chemoreceptors. Annals of the New York Academy of Science 109: 682-695, 1963

60. Sproule BJ, Mitchell JH, Miller WF: Cardiopulmonary physiological responses to heavy exercise in patients with anemia. Journal of Clinical Investigation 39:378-388, 1960

61. Murray JF: Venous oxygenation and circulatory responses to oxygen inhalation in acute anemia. American Journal of Physiology 207:228-234, 1964

62. Candus D: O_2 aveolar-arterial tension difference after 10 days recumbency in man. Journal of Applied Physiology 23:934-937, 1967

63. Doolan PD, Harper HA, Walter RH, et al: Changes in plasma amino acids and blood oxygen content during dialysis with the Kolff-Merrill artificial kidney. Transactions. American Society for Artificial Internal Organs 2:113-118, 1956

64. Physicians and Staff of YNHH Chronic Hemodialysis Unit: Private communication

65. Patel R: Symptomatic pulmonary emboli from A-V shunts in haemodialyzed patients: experience in two cases. New Zealand Medical Journal 66:800-801, 1967

66. Bates DV, Christie RV: Respiratory Function in Disease. Philadelphia, WB Saunders Co., 1964, pp 360-365

67. Cugell DW, Buchingham WB, Webster JR: The limitations of laboratory methods in the diagnosis of pulmonary embolism. Medical Clinics of North America 51:175-183, 1967

68. Mitchell RA, Singer MM: Respiration and cerebrospinal fluid pH in metabolic acidosis and alkalosis. Journal of Applied Physiology 20:905-911, 1965

69. Fencil V, Miller TB, Pappenheimer JR: Studies on the respiratory response to disturbances of acid-base balance with deductions concerning the ionic composition of cerebral interstitial fluid. American Journal of Physiology 210:459-472, 1966

70. Maher J, Schreiner GE: Hazards and complications of dialysis. New England Journal of Medicine 273:370-380, 1965

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